Appendix A: Overview of studies reviewed

AUTHOR/ JOURNAL/YEAR	TYPE OF STUDY	OUTCOMES STUDIED	PATIENT CHARACTERISTICS	RESULTS	HCFA COMM
American Association of Diabetes Educators (AADE), *Diabetes Educator*, 1997	Position Statement	Discussion of patient characteristics for diabetics likely to benefit from CSII	NA	"CSII should be considered a treatment option because it offers increased lifestyle flexibility and enhanced self-management that improves blood glucose control." pg. 398 "Successful implementation of CSII requires a motivated patient with a range of technical skills and self-management capabilities." pg 397	Article o opinion AADE th should be treatmen for some but not m data to su this asser identify subset of diabetics to benefi CSII.
Birkeland KI, *Diabetic Medicine*, 1998 "Improving glycaemic control with current therapies"	Review Article	Review of methods of obtaining glycemic control in type II diabetics	NA	"Successful treatment of Type 2 diabetes depends on different factors from Type 1" pg 518	Discusse managen options f II diabete focussing combinat injected i therapy a hypoglyc agents. The artic makes no mention

					but a generaliz message warning the dange attempti extrapola conclusio proven fo diabetes II.
Blackett PR, *Diabetes Care*, 1995 "Insulin pump treatment for recurrent ketoacidosis in adolescence"	Letter 4 patients who had frequent hospital admissions were started on CSII	HbA1c frequency of hospital admissions and clinic visits	4 adolescent girls with type I diabetes and frequent hospital admissions age range 12-19 yrs	Results after 1 year of CSII compared to results prior to initiating CSII: Hospital admissions per year = 5 vs 29 ($p<0.05$) Clinic visits per year = 24 vs. 36 ($p<0.05$) HbA1c = 11.9% vs 13.5% no statistically significant difference. (HbA1c was statistically significantly lower than baseline after 6 months of CSII at 8.9%).	Small # c also, ado Author g opinion t "CSII the has a pla managen patients v recurrent admissio DKA. " Only lim provided letter.
Bode BW, Steed RD, Davidson PC, *Diabetes Care*, 1996	Prospective clinical trial (crossover, not randomized not controlled)	compares baseline year of MDI to CSII years 1-4 for:	55 patients w/ type I diabetes mellitus 35 women, 20 men	No significant change in HbA1c between MDI and CSII	Suggests patients experienc episodes severe hypoglyc

	pts who had been on MDI for > 1 yr and had experienced severe hypoglycemia, poor glycemic control, and/or hypoglycemic unawareness were switched to CSII	mean HbA1c, patients' weight, episodes of severe hypoglycemia (defined as hypoglycemia requiring assistance of another person)	mean age 39 years mean duration of diabetes 22 years	statistically significantly fewer episodes of severe hypoglycemia for years 1,2,3,and 4 of CSII compared to MDI DKA events not significantly different	when sw from MD CSII. Ho study ma overestin benefit o because s inclusion require su to use a p >1 yr (pt do not to pump an terminate early are excluded results) a because a of a cont group (be attributed may inclu benefits increased educatio attention health ca providers inherent participa study). Suggeste benefits a might no to the Me populatio study po was muc younger Medicare populatio
Cranston I, Lomas J, et al., *Lancet*, 1994	Prospective clinical trial subjects had	subjective awareness of hypoglycemia	12 male subjects with IDDM and history of hypoglycemia unawareness:	Blood glucose level at which subjects reported	small sub populatio (n=12)

"Restoration of hypoglycaemia awareness in patients with long duration insulin-dependent diabetes"	demonstrated hypoglycemia unawareness before study, baseline measure of psychomotor function and awareness during hypoglycemic states were recorded, subjects then avoided hypoglycemia for three weeks	and performance on a psychomotor test after 3 weeks avoidance of hypoglycemia compared with baseline	unawareness: Group A: 6 subjects with good glycemic control Group B: 6 subjects with poor glycemic control age range 28-55 years duration of IDDM 11-32 years Study conducted in United Kingdom	subjective awareness of hypoglycemia was statistically significantly higher after avoidance of hypoglycemia than at baseline: Group A: 3.4 mmol/L compared to 2.3 mmol/L at baseline p=0.0005. Group B: 3.3 mmol/L compared to 2.4 mmol/L at baseline p=0.015 Deterioration of cognitive function as measured by performance on psychomotor test occurred at blood glucose levels of 2.8 mmol/L for Groups A and B at baseline and after intervention.	subjects significa younger Medicare populatio however, had a lon duration diabetes previous Hypoglyc awarenes are statis significa measure nearly impossib objective corrobor subjects reporting they feel hypoglyc symptom However was no differenc between for the m objective measure impairme cognitive function detected psychom testing. The pote relevance study is t hypoglyc unaware were pro

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Dagogo-Jack S, Rattarasarn C, Cryer PE, *Diabetes*, 1994 "Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM"	Controlled clinical trial The study measured glucose counterregulation and symptomatic response to hypoglycemia at baseline and after 3 days, 3-4 weeks, and 3 months of avoiding hypoglycemia. Intervention was a hyperinsulinemic stepped hypoglycemic clamp technique	Symptoms of hypoglycemia glucose counterregulation to correct hypoglycemia; epinephrine, norepinephrine, glucagon and cortisol responses.	6 subjects without diabetes, mean age 24 years 6 subjects with type I diabetes and history of hypoglycemia unawareness, mean age 26 years, mean duration of diabetes 15 years 6 subjects with type I diabetes and awareness of hypoglycemia, mean age 28 years, mean duration of diabetes 16 years The diabetic subjects did not have advanced complications of the disease.	In type I diabetics with history of hypoglycemia unawareness, reported symptoms in response to hypoglycemia increased from baseline after avoidance of hypoglycemia for 3 days (p=0.0034), 3-4 weeks (p=0.0003) and 3 months (p=0.0001). After 3-4 weeks of hypoglycemia avoidance, previously unaware subjects had no statistically significant difference in symptom scores than the nondiabetic controls (no data provided	Small stu populatio comprise fairly you patients Authors data to "s that the syndrom hypoglyc unawaren reversibl that the syndrom defective counterre may not reversibl avoidanc iatrogeni hypoglyc patients IDDM" p 1430-143 The pote relevance study is t the propo reversibi hypoglyc unawaren proves tr

				to compare to the other group of diabetics w/o a history of hypoglycemia unawareness). After avoidance of hypoglycemia the group of diabetics with history of unawareness had no statistically significant increase in epinephrine, pancreatic polypeptide, glucagon, growth hormone, cortisol, or norepinephrine responses to hypoglycemia.	older dia with long duration disease, a of unawa might no preclude CSII.
Emilien G, Maloteaux JM, Ponchon M, *Pharmacological Diabetes Management*, 1999 Pharmacological management of diabetes: recent progress and future perspective in daily drug treatment	Review Article	Background information on diabetes and pharmacologic management of diabetes	NA	pg. 46 although CSII is "neither available nor appropriate for the majority of patients with Type I diabetes, this approach probably brings us as close to achieving optimum glycaemic control, as is feasible with	Article p useful backgrou informati diabetes managen However article do provide e specific c regarding determin what circumsta CSII wou benefit to patients.

				current treatment methods."	
Fanelli CG, Epifano L, Rambotti AM, et al., *Diabetes*, 1993 "Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitudes of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia intensively treated patients with short-term IDDM"	Prospective clinical trial not controlled not randomized subjects were assessed at baseline, then after 2 weeks and 3 months of hypoglycemia prevention	cognitive function, neuroendocrine responses, and symptom responses during hypoglycemia	8 subjects with short duration IDDM (<7 years) at baseline patients had hypoglycemia unawareness mean age= 26 yrs 12 nondiabetic volunteer subjects Study conducted in Italy	Results after 3 months preventing hypoglycemia compared to baseline: episodes of hypoglycemia decreased - $p<0.05$ Improved glucagon response to hypoglycemia (no p value Deterioration in cognitive function in response to hypoglycemia (no p value) At same time, glycosylated hemoglobin increased.	small nu patients patients diabetes time - 7 significa shorter t Medicare populati In discus section a point out effect in with long type I di may be d Pts studi short per time. Co less than comparis non-diab to simila diabetics the interv The artic to provid values fo likelihoo statistica significa differenc glucagon cognitive function. The pote relevance article is

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Farkas-Hirsch R, Hirsch IB, *Diabetes Spectrum*, 1994 "Continuous subcutaneous insulin infusion: a review of the past and its implementation for the future"	Review/opinion	NA	NA	Authors suggest that hypoglycemia unawareness should be considered an indication for CSII because insulin absorption is more predictable when using CSII. Article states authors opinion that CSII allows for "improved diabetes management with the best flexibility of the available options"	Provides proposed indicatio CSII. Contradi authors b stating th with hypoglyc unawaren likely to from CS Remarks authors h used CSI success o 65 yrs.
Hirsch IB, Farkas-Hirsch R, Skyler JS, *Diabetes Care*, 1990 "Intensive Insulin Therapy for Treatment of Type I Diabetics"	Review Article	Discusses intensive therapy of type I diabetes.	NA	"The most precise way to mimic normal insulin secretion clinically is to use an insulin pump in a CSII program. The pump delivers microliter	Overall, excellent discussio elements intensive programs useful di of the pharmac of insulin delivery

				amounts of regular insulin on a continual basis, thus replicating basal insulin secretion."	CSII.
Hirsch IB, Farkas-Hirsch R, Cryer PE, *Diab. Nutr. Metab*., 1991 "Continuous subcutaneous insulin infusion for the treatment of diabetic patients with hypoglycemia unawareness"	Two Case studies At baseline patients were treated with insulin injections and experienced frequent episodes of hypoglycemia with unawareness. Both patients were switched to CSII and HbA1c and frequency of hypoglycemia were reassessed.	Episodes of severe hypoglycemia (defined as requiring glucagon administration). HbA1c	2 patients Case 1: 41 yo man w/ 34 year history of type I diabetes Case 2: 30 yo woman w/ 20 year history of type I diabetes	Case 1: at baseline >5 episodes of severe hypoglycemia per month and mean HbA1c = 11.2%. After initiation of CSII no episodes of severe hypoglycemia mean HbA1c = 11.0%. Case 2: At baseline overall frequency of hypoglycemia not provided but 4 wks with daily episodes. Mean HbA1c = 9.9%. In the 5 months following initiation of CSII patient experienced 2 episodes of severe hypoglycemia. Mean HbA1c = 11.1%	Only 2 pa studied s not possi conclude CSII will occurren severe hypoglyc all patien the study suggest t benefit e some pat Of note, did have duration disease.

Klein, R *Diabetes Care*, 1995 "Hyperglycemia and Microvascular and Macrovascular Disease in Diabetes"	Review article	discussion of recent studies	NA	"It is not certain whether the findings from the DCCT regarding intensive insulin treatment for the control of hyperglycemia to prevent complications of diabetes in people with NIDDM need to be studied in a clinical trial before a rec can be made"	Excellen discussio hypergly and diab complica Emphasi studies o cannot y generaliz Type II d Points ou VA study actually s an increa of death secondar cardiova disease i group of with NID treated w intensive therapy compare group tre with conventi therapy.
Koivisto VA,Yki-Jarvinen H, Helve E et al., *Diabetes*, 1986 "Pathogenesis and prevention of the dawn phenomenon in diabetic patients treated with CSII"	Prospective clinical trial At baseline the diabetic subjects employed CSII with a constant basal infusion rate. 10 of the 12 subjects were noted to have dawn phenomenon (based on glucose measurements	Occurrence of the dawn phenomenon (early morning rise in blood glucose in diabetic patients). The study employs a quantitative definition of the dawn phenomenon: a rise in blood glucose at least two times greater	12 patients with type I diabetes 11 men, 1 woman mean age 30 yrs mean duration of diabetes 11 yrs all patients used CSII for at least 1 month before study 8 controls all men	In patients with dawn phenomenon increasing rate of nocturnal insulin delivery leads to lower morning blood glucose level than maintaining constant basal insulin infusion rate through the night (no p value). Increasing	The stud suggests increasin nocturna insulin i can preve occurren dawn phenome However of the st be limite informati a clinical , small s populatio 10 patien

	during in hospital monitoring compared to similar monitoring of control group) For the 10 diabetics with demonstrated dawn phenomenon the nocturnal basal insulin infusion rate was increased and glucose measurements repeated.	than that in healthy subjects.	not diabetic mean age 28 yrs	nocturnal insulin delivery caused decreased early morning glucose production compared to constant basal infusion rate ($p<0.05$)	baseline phenome study po was your had short duration disease t Medicare populatio
Ohkubo Y, Kishikawa H, Araki E, et al., Diabetes Research and Clinical Practice, 1995. "Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study."	Randomized clinical trial subjects randomly assigned to multiple insulin injection treatment (MIT) group using three or more daily injections of insulin and conventional insulin treatment (CIT) group using one or two daily injections of insulin. Study followed patients for 6 years: 110 pts at start of study and 102 pts	Progression of retinopathy, nephropathy, neuropathy	110 patients with type II diabetes all patients were under 70 years old (mean age ~ 49) and were otherwise healthy 2 cohorts primary prevention: 55 patients w/o retinopathy or urinary albumin excretion >30 mg/24 hr at baseline secondary prevention cohort: 55 patients w/ retinopathy and urinary albumin excretion <300 mg/24hr Study conducted in Japan	Combined cohorts: HbA1c lower for MIT than CIT $p<0.001$ Statistically significant difference for median nerve conduction velocities- increased for MIT and decreased for CIT. Pts experiencing mild hypoglycemic reactions 6 for MIT, 4 for CIT.	Study co on insuli requiring diabetics "the sign of intens insulin th patients NIDDM been wel evaluate 104) Patient populatio studied w limited t than 70 y and othe healthy. patients very adv diabetic complica

	at completion.			primary prevention cohort: development of: retinopathy lower in MIT than CIT (7.7% vs. 32%, p=0.039) nephropathy lower in MIT than CIT (7.7% vs 28%, p=0.032) secondary prevention cohort: progression of: retinopathy lower in MIT than CIT (19.2% vs. 44%, p=0.049). Nephropathy lower in MIT than CIT (11.5% vs. 32%, p=0.044).	In conclu authors n benefit o intensive therapy f II diabeti advanced microvas complica not yet establish 115). Study co in Japan significar differenc between Japanese Americar and impo role of di control o diabetes, results m apply to Medicare beneficia most of v consume much dif from the in the stu Needs to replicate
Reichard P, Nilsson BY, Rosenquist U, *NEJM*, 1993 "The effect of long-term intensified insulin treatment on the development	Randomized controlled trial 54 patients assigned to standard insulin treatment 48 patients assigned to intensified	glycemic control microvascular complications	102 patients with type I diabetes mean age = 30 years at baseline patients had nonproliferative retinopathy, normal serum creatinine, and poor blood glucose control	HbA1c lower in intensive treatment group (p=0.001) episodes of serious hypoglycemia - 1.1 episodes per patient year	study obt statistica significar results fo progressi several m of microv complica intensive standard therapy

of microvascular complications of diabetes mellitus"	insulin treatment Main difference between groups was that intensive group received more diabetes education and greater contact with health care providers, some patients in each group received three or more daily injections of insulin and some in each group took two or fewer injections of insulin. NO subjects used CSII Pts followed for 18 months, 3, yrs, 5 yrs, 7.5 yrs		control Study conducted in Stockholm	in intensive group, 0.4 in standard group some measures of microvascular complications statistically significantly less pronounced in intensive group than in standard group: Percent of patients who developed serious retinopathy= 27% of intensive treatment group and 52 % of standard treatment group (p=0.01) decrease in visual acuity = 14% of intensive treatment group and 35% of standard treatment group (p=0.02) development of nephropathy, 1 patient in intensive treatment group and 9 patients in	therapy study sub were muc younger Medicare populatio age 30 ye episodes serious hypoglyc (defined requiring from som else) seer than othe studies, a statistica analysis differenc between This stud employs different terminol most stu this field patients i standard took thre more inje of insulin (which w considere in many while so patients i intensive took only injection insulin p (which w considere conventi

				standard treatment group (p=0.01) slowing of nerve conduction velocity (p=0.007, 0.003, and 0.02, for three different nerves) No statistically significant difference between groups for symptoms of peripheral neuropathy.	therapy b studies). the differ between may repr the effect educatio frequenc injection insulin. Of note, with inte treatmen glycosyla hemoglo remained normal ra
Wang PH, Lau J, Chalmers TC, *Lancet*, 1993 "Meta-analysis of effects of intensive blood-glucose control on late complications of type I diabetes"	Meta-analysis results of 16 randomized trials of intensive therapy (MDI or CSII) in type I diabetics with conventional therapy (1 or 2 daily injections of insulin).	progression of diabetic retinopathy and nephropathy, and risks of severe adverse effects	patients with type I diabetes no information regarding number of pts, age, duration of disease	intensive therapy may cause more frequent severe hypoglycemic reactions than conventional therapy but statistically significant difference not established. CSII cohorts experienced 12.6 more episodes of DKA per 100 person-years compared to conventional therapy (95% C.I. 8.7-16.5).	Not mucl informati about sub comprisi study pop except th are type diabetics Does not data usef comparin with MD

				No comparison to MDI provided. Long term intensive therapy lower risk of progression of nephropathy ($p<0.001$) and retinopathy ($p=0.011$)	
Whitehouse FW, *Diabetic Medicine*, 1997 "Insulin therapy and its shortcomings - the need for new approaches"	Review Article	Review of therapies of diabetes	NA	Author states Amylin replacement may also help glycemic control in diabetics. pg. 56 "it has not been possible to restore normal glycemic control in such patients (with diabetes mellitus), despite strategies such as intensive therapy with or without CSII."	Article d current tr of diabet suggests addition amylin replacem therapy r facilitate glycemic Author c Bode, St Davidson to sugges CSII pro tight glyc control w reduced r severe hypoglyc compared MDI.
Wredling R, Hannerz L, Johansson UB, *Practical Diabetes Int,* 1997 Variability of blood	Prospective clinical trial (not randomized, not controlled) Patients were treated with MDI therapy involving 4 or 5	Fluctuation of blood glucose levels.	21 subjects with type 1 diabetes mean age 41 years age range 31-45 yrs mean duration of diabetes 19 yrs	Results were based on patients' self monitoring of blood glucose. Mean blood glucose level was lower	The study decreased fluctuatio blood glu levels for subjects complied the strict monitori

glucose levels in patients treated with continuous subcutaneous insulin infusion: a pilot study	subcutaneous insulin injections per day for 6 months and then were switched over to CSII. Subjects were required to self monitor blood glucose levels 5 times per day during both phases of the study.		diabetes 19 yrs Results were reported only for the 14 of 21 subjects who acceptably completed the blood glucose monitoring protocols over the course of the study. Limited information regarding subject selection criteria beyond the fact that the subjects were all patients selected for CSII treatment.	using CSII than MDI (9.3 mmol/L vs. 11.2 mmol/L, $p<0.01$) as was HbA1c (7% vs. 8%, $p<0.01$). Variability in blood glucose measured as the mean standard deviation of the blood glucose measurements was lower during CSII than MDI (3.6 mmol/L vs. 4.9 mmol/L, $p<0.01$) The authors conclude that patients with great fluctuations in blood glucose levels might benefit from initiation of CSII.	protocols However not demo that these differenc exerted a significa clinical b Also, the may not generaliz the gener populatio